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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,757	09/24/2003	Alan Klotz	10211.200-US	4235

25907 7590 08/05/2005

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,757	KLOTZ ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,24,32,36,52,53,60-64,68,69,92,100,104,120,121 and 128-130* is/are pending in the application.

4a) Of the above claim(s) *62-64,68,69,92,100,104,120,121,128 and 129* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,24,32,36,52,53,60,61 and 130* is/are rejected.

7)☒ Claim(s) *36,61 and 130* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0104*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.08

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Applicant's election, with traverse, of Invention I, Claims 1, 24, 36, 52, 53, 60, 61, and 130 and variants having mutations at residues 144, 193, 198, 201, 218, 223, and 227-231, deletion of residues 192, 197, and 226, and an insertion between residues 224 and 225, in their response of June 28, 2005, is acknowledged. The traversal is on the grounds that no undue burden would be imposed by examination of Invention I and II and all of Inventions (A)-(P).

The traversal is not found persuasive. The MPEP states: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02" (see MPEP 803). The reasons searching more than one of Inventions I-III and (A)-(ZZZ...) would be a burden on the Office were clearly explained in the prior action. In brief, Invention I, class 435, subclass 212, would not encompass a search for Invention I, class 536, subclass 23.2, which represent different fields of search. Inventions (A)-(ZZZ...), as indicated represent an essentially unlimited number of sequences and, thus, searching all of said sequences would be an undue burden on the office. The requirement is still deemed proper and is therefore made FINAL.

It is acknowledged that Applicants have cancelled Claims 2-23, 25-31, 33-35, 37-51, 54-59, 65-67, 70-91, 93-99, 101-103, 105-119, and 122-127. Claims 1, 24, 32, 36, 52, 53, 60-64, 68, 69, 92, 100, 104, 120, 121, and 128-130 are pending. Claims 62-64, 68, 69, 92, 100, 104,

120, 121, 128, and 129 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 24, 32, 36, 52, 53, 60, 61, and 130 are examined on their merits.

Specification-Objections

Abstract

It is noted that the Abstract lists amino acid substitution merely by residue number, except for residue 193, which is listed as the specific substitution S193A. The Examiner questions whether such inconsistency was Applicant's intention.

Claims-Objections

Claims 36, 61, and 130 are objected to for having improper antecedent usage as follows.

Claim 36: "the insertion G224GT" has no antecedent basis.

Claim 61: the phrases "the form of a precursor" and "the prepro region" have no antecedent basis.

Claim 130: "a variant of claim 1" should be "the variant of claim 1".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 24, 36, 52, 53, 61, and 130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

The phrase "corresponding to positions...of SEQ ID NO: 2" renders Claim 1 indefinite. It is unclear whether the scope of Claim 1 encompasses only variants of the protein set forth by

SEQ ID NO: 2 or variants of any protein having residues corresponding to those in SEQ ID NO: 2. A person of ordinary skill in the art would not know the metes and bound of the recited invention. Claims 24, 36, 52, 53, 60, 61, and 130, as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons. For purposes of examination, it is assumed that Claim 1 is meant to recite a variant of any protein in which residues corresponding to those of SEQ ID NO: 2 are modified.

Claim 1 is indefinite in the recitation of "hybridizes under at least low stringency conditions" as this term is unclear absent a statement of the conditions under which the hybridization reaction is preformed. Nucleic acids that will hybridize under some hybridization conditions, will not necessarily hybridize under different conditions. The hybridization conditions described on page 10 lines 22- 30 are only exemplary and do not define the conditions recited in Claim 1. Thus, Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 24, 36, 52, 53, 60, 61, and 130, as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons.

Claims 32 and 36 are rendered indefinite by "V192*" "K197*", and "A226*". A person of ordinary skill in the art would not know the metes and bound of the recited invention.

Claims 52 and 53 are rendered indefinite by the phrase "preferably". It is unclear whether the limitations preceding the phrase are part of the claimed invention. See MPEP § 2173.05(d).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP §

2173.05(c). In the present instance, Claim 52 recites the broad recitation "the total number of substitution is 11" and the claim also recites "more preferably 10, even more preferably 9,...", which is the narrower statement of the range/limitation. Claim 52 is thus rendered indefinite. Likewise, Claim 53 is rendered indefinite by reciting the broad range of "total number of deletions is 3" and also reciting the narrow limitations of "more preferably 2...". Thus, Claims 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1, 24, 36, 52, 53, 61, and 130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the variant of SEQ ID NO: 2, wherein said variant has the substitutions V144T, S193A, D198S, Q201M, A218I, N223S, or R227S, P228T, N229S, Y230T, and S231P, deletion of residues 192, 197, and 226, and insertion of a threonine between residues 224 and 225 and has chymotrypsin-like activity (Fig 6), does not reasonably provide enablement for any variant of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has a substitution, relative to SEQ ID NO: 2, at one or more of residues corresponding to 144, 193, 198, 201, 218, 223, or 227-231, a deletion at one or more of residues corresponding to 192, 197, or 226, and an insertion between residues 224 and 225 and has either (a) 70% homology to residues 25-248 of SEQ ID NO: 2 or (b) hybridizes to residues 202-801 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 52, 53, 61, and 130 are so broad as to encompass any variant of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to 144, 193, 198, 201, 218, 223, or 227-231, a deletion at one or more of residues corresponding to 192, 197, or 226, and an insertion between residues 224 and 225 and has either 70% homology to residues 25-248 of SEQ ID NO: 2 or hybridizes to residues 202-801 of SEQ ID NO: 1. Claim 24 is so broad as to encompass any variant of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to V144T, S193A, D198S, Q201M, A218I, N223S, or R227S, P228T, N229S, Y230T, or S231P, a deletion

at one or more of residues corresponding to 192, 197, or 226, and an insertion between residues 224 and 225 and has either (a) 70% homology to residues 25-248 of SEQ ID NO: 2 or (b) hybridizes to residues 202-801 of SEQ ID NO: 1. Claim 32 is so broad as to encompass any variant of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to V144T, S193A, D198S, Q201M, A218I, N223S, or R227S, P228T, N229S, Y230T, or S231P, a deletion at one or more of residues corresponding to V192*, K197*, or A226*, and an insertion between residues 224 and 225 and has either (a) 70% homology to residues 25-248 of SEQ ID NO: 2 or (b) hybridizes to residues 202-801 of SEQ ID NO: 1. Claim 36 is so broad as to encompass any variant of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to V144T, S193A, D198S, Q201M, A218I, N223S, or R227S, P228T, N229S, Y230T, or S231P, a deletion at one or more of residues corresponding to V192*, K197*, or A226*, and an insertion between of a threonine between residues 224 and 225 and has either (a) 70% homology to residues 25-248 of SEQ ID NO: 2 or (b) hybridizes to residues 202-801 of SEQ ID NO: 1. (Note Examiner's rejection above of Claims 32 and 36 under 35 USC 112, second paragraph because "*" renders the claim indefinite.) The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired chymotrypsin-like activity requires a knowledge of and guidance with regard to which amino acids in the protein's

sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO: 2 and the nucleotide sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques as well as assays for chymotrypsin activity are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Wishart et al, 1995; Witkowski et al, 1999). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1, 24, 36, 52, 53, 61, and 130, which encompass the microbial trypsin variants described above, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the chymotrypsin activity; (B) the general tolerance of the chymotrypsin activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including any number of polypeptide variants having chymotrypsin activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 60 is rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The invention of Claim 60 appears to employ a novel vector. Since the vector is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmid's sequence is not fully disclosed, nor have all the sequences required for its construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmid. The specification does not disclose a repeatable process to obtain the vector and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the organisms but there is no indication in the specification as to public availability. If the deposit is/was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited

under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

Written Description

Claims 1, 24, 36, 52, 53, 61, and 130 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of polypeptide having chymotrypsin-like activity, wherein the polypeptide has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to 144, 193, 198, 201, 218, 223, or 227-231, a deletion at one or more of residues corresponding to 192, 197, or 226, an insertion between residues 224 and 225, and has either (a)

70% homology to residues 25-248 of SEQ ID NO: 2 or (b) hybridizes to residues 202-801 of SEQ ID NO: 1. The specification teaches the structure of only a single representative species of such polypeptides. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having chymotrypsin-like activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.

Art Unit 1656

SHERIDAN SWOPE, Ph.D.
PATENT EXAMINER